REMARKS

Claims 1, 3-15, 22-29, 43, 45, and 47-50 are pending after the amendments made herein.

Claims 2, 16-21, 30-42, 46 and 51-54 are cancelled.

In this response, the specification is amended to delete reference to 72 kd as the size of the target antigen of the murine or chimeric 31.1 monoclonal antibodies, because recent experiments have shown this molecular weight to be in error. See the accompanying Fasick 2006 Declaration. These amendments are necessary to correct an inaccuracy made by inadvertent error in United States Patent 5,688,657 ("the '657 Patent") (37 C.F.R. §1.173(f)).

Claim 2 is canceled to cancel subject matter relating to antibodies which bind specifically to a colon carcinoma-associated epitope that specifically binds to monoclonal antibody 33.28 other than antibody 33.28 or a chimeric antibody derived therefrom.

Claims 3, 6, 7, 8, 10, 11, 12, 22 and 30 are amended to delete reference to cancelled claim 2.

Claim 5 is amended and 44 is deleted in this response to delete reference to the 72 kd size of the target antigen and to cancel subject matter relating to antibodies that generally competitively inhibit binding of the deposited antibodies.

Claim 5 is amended to cover antibodies which share an antigen-binding region with murine monoclonal antibody 31.1 (such as, for example, the deposited Chi #1 chimeric antibody) or 33.28. This amendment is supported by the instant specification at column 7 lines 14-20, which state:

> The chimeric antibodies of the invention comprise individual chimeric heavy (H) and light (L) immunoglobulin chains. The chimeric H chain comprises an antigen-binding region derived from the H chain of a non-human antibody specific for the epitope recognized by 33.28 or 31.1, which is linked to at least a portion of a human H chain C region (C_H).

This amendment to claim 5 therefore does not constitute new matter and is a narrowing limitation relative to, for example, original claim 42.

Claims 30-41 are cancelled because they relate to antibodies that are functionally but not necessarily structurally related to the deposited antibodies.

Claim 50 is amended to include "(c)" to denote the subparagraph referring to immunoperoxidase, where "(c)" was apparently inadvertently omitted, (a), (b) and (d) being recited. See also analogous claims 28 and 29.

None of the foregoing new amendments constitutes new matter, and each is made to correct an inadvertent error in the '657 Patent.

The amendments made previously in this reissue application are included above, but were explained in previous submissions to the Patent Office by Applicants. All of these explanations (including but not limited to Amendments/Responses submitted by Applicants dated November 16, 2005, August 10, 2005, June 17, 2005, and November 5, 2004) are incorporated herein by reference. In short, each of the amendments to the specification and claims are made to correct an inadvertent error made without deceptive intent.

A Supplemental Reissue Declaration averring that "[e]very error in the patent which was corrected in the present reissue application, and is not covered by a prior oath/declaration submitted in this application, arose without any deceptive intention on the part of the applicant."

A number of rejections and objections have been raised against the pending claims. For reasons set forth in detail below, these rejections and objections should be removed and the claims should be allowed to issue.

1. The Claims Cover Statutory Subject Matter

Claim 53 is rejected under 35 U.S.C. §101 because, according to the Examiner, the rejected claim does not sufficiently distinguish over antibodies as they exist in nature. The Examiner states that amending the claims to refer to an "isolated" of "purified" antibody would obviate the rejection. (Official Action mailed December 17, 2004).

Claim 53 is cancelled, so that the basis for this rejection is obviated, and the rejection should be removed.

2. The Claims Are Not Anticipated

Claims 5-6, 23, 51-52 are rejected under 35 U.S.C. §102(b) as anticipated by Hollinshead et al., (Cancer, 1985, 65:480-489, henceforth *Hollinshead*), as set forth in the previous Official Action, Hollinshead discloses a monoclonal antibody to a colon carcinoma antigen having a molecular weight of 72 kilodaltons which is not present in normal tissue. "It is the Examiner's position that Hollinshead et al. have produced hybridomas which secrete antibodies that are directed to the same antigen that the claimed antibodies bind."

Of note, the rejection was originally applied to claims 5,6, 23, 51 and 52, which, as then amended, covered antibodies which need not be structurally related to the deposited antibodies, but rather shared the same functional property of recognizing the same epitope and/or antigen. The claims have been amended to remove antibodies which are not structurally related to the deposited antibodies. Therefore, the basis for this rejection has been obviated and should be removed.

3. The Claims Are Not Obvious

Claims 5-15, 23, 30-33 and 51-52 are rejected as being allegedly obvious over *Hollinshead* and in view of Neuberger et al., (WO 86/05133, published 03/1986, henceforth *Neuberger*), for reasons of record. According to the Examiner:

> One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have labeled the antibody in view of Hollinshead et al. and Neuberger et al. because Hollinshead et al. teach the antigen is of molecular weight 72 kd and the antigen is a colon carcinoma associated antigen and an ELISA for detection of the antigen was performed and the antibody was labeled with an enzyme. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have labeled the antibody in view of Hollinshead et al. and Neuberger et al. because Neuberger et al. teach labeling of antibodies for detection and treatment with cytotoxic agents and radiolabels of antibodies. Thus, it would have been

obvious to one of ordinary skill in the art to produce an antibody which is a labeled antibody to the antigen of Hollinshead in view of Neuberger et al.

Applicants assert that the amended claims are not obvious over *Hollinshead* in view of *Neuberger*. As in the anticipation rejection discussed in the preceding section, the claims, when rejected, encompassed antibodies which are functionally but not necessarily structurally related to the deposited antibodies. As the claims have been amended to delete this subject matter, the basis for the rejection has been obviated and the rejection should be removed.

4. The Claims Are Fully Compliant With 35 U.S.C. § 112, first paragraph

A. The Claims Are Enabled

Claims 1-15, 22-24, 43-45 and 47-54 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Examiner states that:

> The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide enabling disclosure without complete evidence that either the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.
>
> Applicant's referral to the deposits of PCA 33.28 and PCA 31.1 on 8/26/03 is an insufficient assurance that the required deposit has been made and that all the conditions of 37 C.F.R. 1.801-1.809 have been met. This is especially insufficient assurance that the required deposits have been met in view of the amendment filed 6/20/05, which states on page 4-5 (referring to the "Fasick Declaration") that "the hybridoma cells deposited for this reissue application did not react with the expected (70kDa) sized protein in a tumor antigen sample. Thus there is a question as to whether the correct hybridoma was deposited. Applicant further

indicates that the issue is being further investigated for both antibodies. (emphasis in original)

Applicants assert that the Fasick 2006 Declaration, which provides an update regarding the antigen specificity data, provides sufficient evidence that the correct hybridomas have in fact been deposited. Paragraphs 6-9 of the Fasick 2006 declaration state as follows:

> 6. In this declaration, I report the results of subsequently performed experiments, performed by me or under my direction, which have repeated and confirmed the result reported in my previous declaration. The results of one such experiment are presented in Figure 1 (Exhibit 4). In a Western blot of cell lysates from ASPc1 (a human pancreatic cancer derived cell line) and LS147T (a human colon carcinoma derived cell line), an approximately 40 kd band was detected by both chimeric 31.1 antibody (upper panel) and murine 31.1 antibody from PTA-2497 hybridoma (lower panel).
>
> 7. Chimeric 31.1 antibody is an accurate representation of the antigen specificity of the original murine 31.1 monoclonal antibody disclosed in the '657 patent because it is derived from that original murine 31.1 antibody. A cell line producing the chimeric version of 31.1 antibody was deposited with the American Type Culture Collection during the original prosecution of the '657 patent, where it was referred to as "Chi #1" and assigned Accession No. CRL 12316 (in the '657 patent specification, column 3 lines 65-67). The identity of that deposit was never questioned, and Chi#1 was *not* re-deposited. The recent experimental results presented in Figure 1 (Exhibit 4) show chimeric 31.1 reacting with colon cancer derived cell line LS174T; consistent with these results, the '657 patent discloses that Chi#1 stained LS174 in cytofluorometry studies and lysed LS174T cells in antibody-dependent cell-mediated cytotoxicity tests. Therefore there is no reason to doubt that

the Chi#1 antibody used to generate Figure 1 (Exhibit 4) correctly represents the original murine 31.1 antibody specificity.

8. That the chimeric 31.1 and the re-deposited murine 31.1 antibodies both bind to the same size antigen in two different cancer cell lines demonstrates, in my opinion, that (i) the re-deposited murine 31.1 hybridoma is correct and represents the original disclosure of the '657 patent and (ii) the size of the target antigen, originally reported to be about 72 kilodaltons, was in error.

9. Further, experiments have now been performed to verify the correctness of the re-deposited 33.28 hybridoma. As seen in Figure 2 (Exhibit 5), an approximately 60-70 kd band was detected by antibody prepared [from] a sample of 33.28 hybridoma cells stored at IBS (upper panel) as well as 33.28 antibody produced by re-deposited hybridoma PTA-5413 (lower panel) in the lane containing cell lysates from WiDR cells (human colon carcinoma derived cell line). In my opinion, the observed antigen size in these recent experiments is consistent with the size disclosed in the '657 patent, 61.1 kd. This, together with the fact that antibody produced by both company-stored and re-deposited hybridomas reacted with the same size antigen, demonstrate to me that the re-deposit of 33.28 hybridoma cells is correct.

Thus Dr. Fasick's findings indicate that the re-deposits of hybridomas designated PCA 31.1 and PCA 33.28, which produce monoclonal antibodies 31.1 and 33.28, respectively, possess the same specificity as described in the Application as filed, and therefore are correct. That said, however, the data also reveals that the '657 patent provided an inaccurate molecular weight, 72 kd, for its target antigen. Applicants have deleted recitation of this inaccurate molecular weight from the specification and claims. Of note, the crux of the invention lies in the ability of 31.1 antibodies to recognize a tumor associated antigen. As the murine and chimeric 31.1 monoclonal antibodies have a

defined structure themselves, their target antigen is defined by these antibodies, whatever its molecular weight may be.

In view of the above Declaration and amendments, the rejection under 35 U.S.C. § 112, first paragraph should be removed.

B. The Claims Comply With The Written Description Requirement

Claims 2-3, 5-15, 23-24, 30-33 and 51-52 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of compliance with the written description requirement. The Examiner states that:

> No support is found for a purified antibody "which competitively inhibits binding" of mAb 33.28, 31.1 and Chi#1.

The amended claims no longer contain the objected to phrase, so that the basis for the rejection is obviated and it should be removed.

CONCLUSION

For all the foregoing reasons, the rejections should be removed and the claims should be allowed to issue.

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